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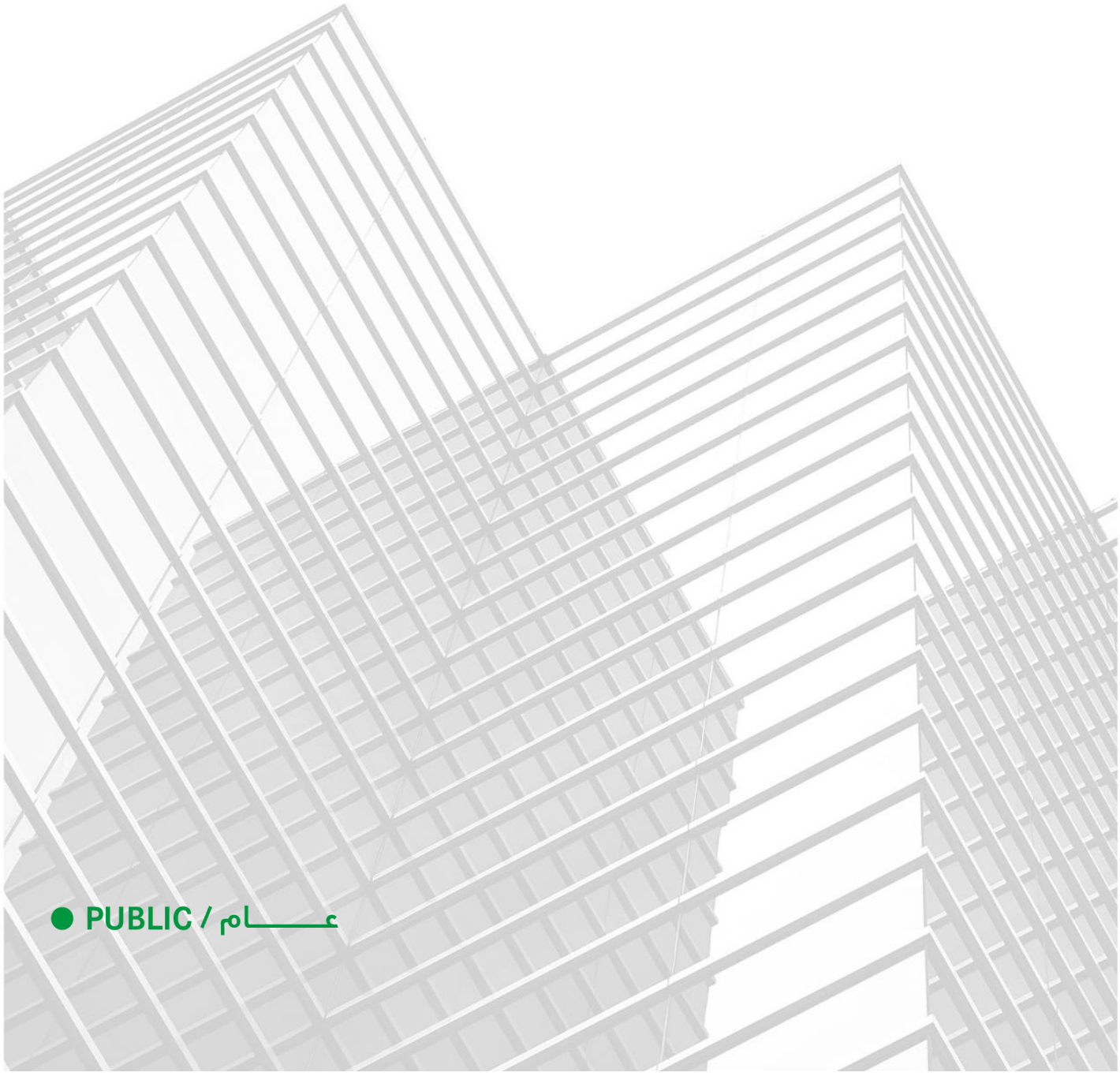
DEPARTMENT OF HEALTH

Inherited Retinal Disorders Genetic Testing and Management Guideline



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1.Guideline Purpose and Brief

The purpose of this guideline is to standardize the practice of genetic testing for inherited retinal disorders for clinical management of cases including diagnosis and treatment selection.

This guideline aims to provide guidance on genetic testing for inherited retinal disorders and is intended for use by clinical specialties in ophthalmology. It will provide criteria for individuals in which genetic testing is indicated. The management of identified variants associated with inherited retinal disorders and additional information on clinical management are detailed within this guideline.

2. Definitions

No.	Term / Abbreviation	Definition
2.1	Autosomal dominant	A pattern of inheritance where a single copy of a mutated gene causes a genetic disorder.
2.2	Autosomal recessive	A pattern of inheritance in which both copies of the gene need to be defective to cause the condition as having only one copy of the mutation is not enough for symptoms to occur. Typically, one defective allele is inherited from each parent.
2.3	Cone Cell	Conical shaped photoreceptors that operate best in high intensity lighting and are responsible for the perception of color
2.4	Food and Drug Administration (FDA)	An agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines, and other biological products for human use, and medical devices.
2.5	Gene Therapy	Gene therapy is an experimental treatment using genetic material to treat or prevent certain diseases.
2.6	Hyperopia	Farsightedness
2.7	Low vision rehabilitation	Aims to optimize the use of residual vision after severe vision loss, but also aims to teach skills to improve visual functioning in daily life
2.8	Mutation	An alteration in the nucleic acid sequence of the genome of an organism
2.9	Nyctalopia	Night blindness which makes it difficult to see in dark places or for eyes to adjust to sudden changes between bright light and darkness.
2.10	Nystagmus	Involuntary rapid repetitive rhythmic movements of the eyes
2.11	Photophobia	An increased sensitivity to light
2.12	Photoreceptor	Cells located in the retina that can convert light into an electrical signal

2.13	Phototransduction	The process by which light entering the eye is converted into electrical signals that are transmitted to the brain
2.14	Retinitis pigmentosa	A degeneration of the rods and then the cones of the retina resulting in night blindness and progressive contraction of the visual field
2.15	Rod Cell	Cylindrical shaped photoreceptors in the retina that are responsible for low light and peripheral vision
2.16	X-linked	X-linked inheritance indicates that a gene responsible for a genetic disorder is located on the X chromosome.
2.17	Polydactyly	A birth defect that causes extra fingers or toes

2. Abbreviations

No.	Term / Abbreviation	Definition
2.18	CHM	Gene that when mutated results in choroideremia, also known as *CHM*-associated retinal degeneration
2.19	ERG	Electroretinography
2.20	FST	Full-field stimulus test
2.21	IRDs	Inherited Retinal Disorders: rare, inherited eye diseases resulting from an abnormality in an individual's genetic makeup
2.22	LCA	Leber congenital amaurosis
2.23	RP	Retinitis Pigmentosa

3.Guideline Content

3.1 Background [1,2,3,4,5,6,7,8,9,10]

3.1.1 Inherited retinal diseases (IRDs) are a group of disorders that can cause severe vision loss or even blindness and are among the most common genetic diseases in humans.

3.1.2 Each IRD is caused by at least one pathogenetic variant in genes that encode proteins critical to retinal function.

3.1.3 Among IRDs, there is significant phenotypic and genotypic overlap. Therefore, genetic testing is a crucial step in obtaining a definitive diagnosis for individuals. This also reveals risk for potential associated disease, allows for identification of potential treatment options for patients, and enables genetic counseling for the patient and his/her entire family.

3.1.4 IRDs can affect individuals of all ages and can be stable or progress at different rates. However, many are degenerative, meaning that symptoms get worse over time.

3.1.5 There are 4 broad classes of IRDs, as illustrated in Figure 1. There are also some miscellaneous forms, not covered by the 4 broad classes. Genetic testing and genetic counseling are essential components in the management of patients with IRDs as

genetic testing can confirm the diagnosis, provide information to optimize management of the patient and family members, and determine eligibility to participate in clinical trials.

3.1.6 Genetic testing and genetic counseling methods for identifying the genetic cause of IRDs have advanced significantly in recent years. Causative mutations can be identified in up to 56-76% of patients with IRDs. Even higher mutation detection rates are found in the Arabian Gulf.

3.1.7 Genetic testing is appropriate for most patients with clinically diagnosed genetic retinal degeneration. Determination for testing should be made by a clinical geneticist, genetic counselor, or clinician with experience in genetics.

3.1.8 At risk family members can also benefit from genetic testing to determine carrier status and for family planning. The implications of genetic testing for asymptomatic individuals should be accompanied by proper genetic counseling.

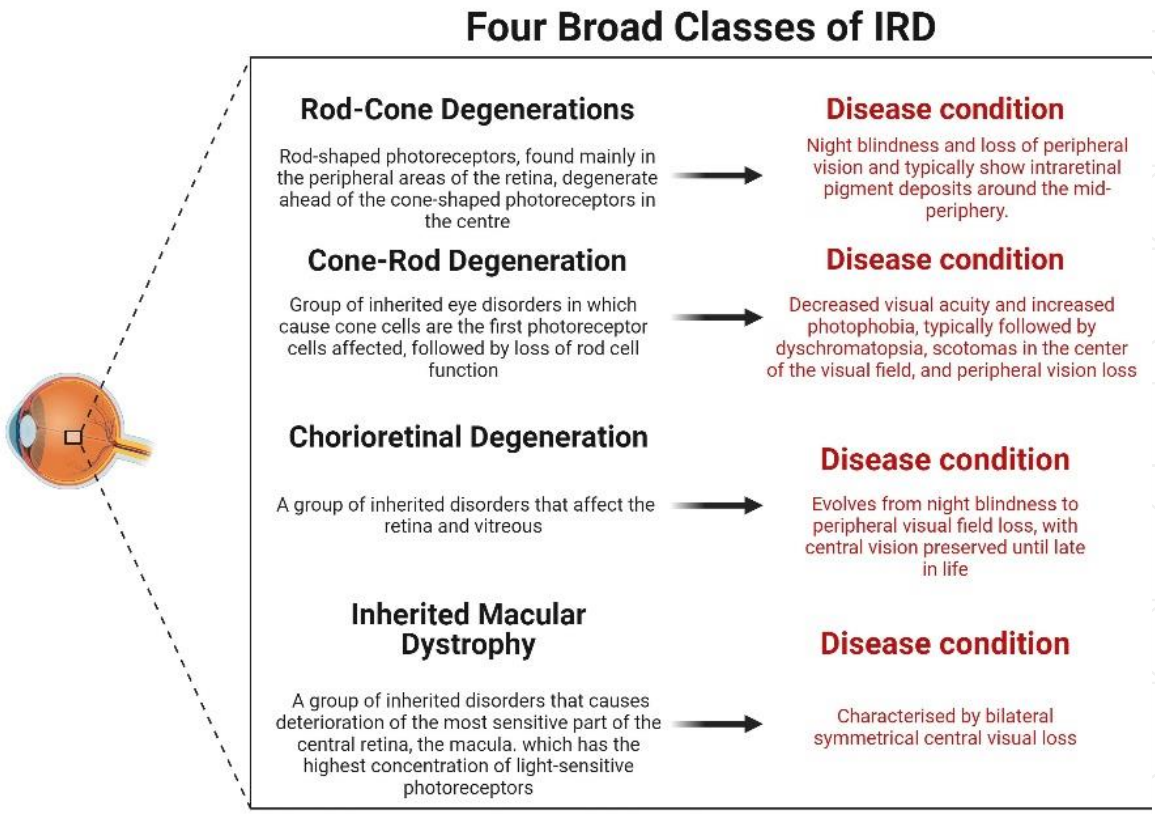

Figure 1: Four Broad Classes of IRD

3.2 Common Inherited Retinal Disorders [9,10,11]

3.2.1 There are over 260 genes that when mutated are known to cause IRDs and over 20 known IRDs, with some diseases still being researched. This guideline provides an overview of common IRDs including their genetic causes, inheritance pattern, and available treatment.

3.2.2 Leber congenital amaurosis (LCA)

3.2.2.1 **Overview:** [11,12]

3.2.2.1.1 LCA, otherwise known as severe early onset retinal degeneration, is a type of pan-retinal degeneration appears at birth or in the first few months of life. Babies with this disorder typically have severe visual impairment. The visual impairment tends to worsen over time.

3.2.2.1.2 This condition affects the retina, which is the specialized tissue at the back of the eye that detects light and color. Associated ocular findings include photophobia, poor night vision, nystagmus, and extreme hyperopia. The pupils, which usually expand and contract

in response to the amount of light entering the eye, often do not react normally to light. Instead, they expand and contract more slowly than normal, react paradoxically, or they may not respond to light at all.

3.2.2.1.3 By definition, LCA is ocular-only disease. However, delayed development and intellectual disability are sometimes associated with LCA.

3.2.2.2 **Genetic Causes and Inheritance Pattern:** [8,11,12]

3.2.2.2.1 At least 20 genetic types of LCA have been described.

3.2.2.2.2 The types are distinguished by their genetic cause, patterns of vision loss, and related eye abnormalities. The variants found in genes causing LCA play a variety of roles in the development and function of the retina. Some of the genes associated with LCA are necessary for the normal development of photoreceptors, while other genes are involved in phototransduction, or the function of cilia found in the retina's photoreceptors which are necessary for vision.

3.2.2.2.3 Variants in any of the genes associated with LCA disrupt the development and function of the retina, resulting in early vision loss. Variants in the *CEP290*, *CRB1*, *GUCY2D*, and *RPE65* genes are the more common causes of LCA reported globally, while variants in other genes generally account for a smaller percentage of cases. In about 30 percent of all people with Leber congenital amaurosis, the cause of the disorder is unknown, though research is ongoing.

3.2.2.2.4 In the Middle East, the most common genetic variant identified were the *TULP1* and *IFT140* genes.

3.2.2.2.5 The majority of LCA cases are inherited in an autosomal recessive pattern.

3.2.2.2.6 LCA caused by variants in the *CRX* or *IMPDH1* genes, are inherited in an autosomal dominant pattern.

3.2.2.3 **Genetic testing:** [11,12,13,14]

3.2.2.3.1 Genetic testing is available to identify the gene causing the disorder and can guide clinicians to the treatment required. As treatment is available for *RPE65* causing LCA, it is essential that genetic testing be offered for patients with LCA who have a phenotype consistent with *RPE65*-related LCA. In addition, genetic testing can reveal syndromic forms of early-onset retinal dystrophy and allow anticipatory management of non-ocular features (e.g., systemic ciliopathies).

3.2.2.4 **Treatment:** [13,14]

3.2.2.4.1 The US FDA approved Luxturna (Voretigene neparvovec), the first gene therapy for LCA in 2017. It is currently only approved to treat LCA caused by mutations to the *RPE65* gene. Further details regarding indication, dosage, and administration are included in Appendix 3.

3.2.3 Retinitis pigmentosa (RP)

3.2.3.1 **Overview:** [8,15,16,17,18,19,20,21]

3.2.3.1.1 RP is a major subset of IRDs. RP causes cells in the retina to break down slowly over time, causing vision loss.

3.2.3.1.2 RP is the most common type of inherited eye disease with symptoms usually presenting in from age 10-40 years, although patients frequently experience nyctalopia in their youth and lose their midperipheral vision in the early adult years. Most individuals with RP lose the majority of their vision over time.

3.2.3.1.3 An early symptom of RP is loss of night vision. Parents may notice that children with RP have trouble moving around in the dark or adjusting to dim light.

3.2.3.1.4 RP also causes loss of peripheral vision and over time, the field of vision narrows until individuals only have some central vision, also called tunnel vision. Some people with RP lose their vision more quickly than others. Eventually, most people with RP lose their side vision and their central vision.

3.2.3.1.5 Other potential symptoms of RP include sensitivity to bright light and loss of color vision.

3.2.3.1.6 Most RP patients meet criteria for legal blindness by age 40 due to narrowing of visual fields.

3.2.3.1.7 RP can be differentiated into syndromic and non-syndromic RP. Non-syndromic RP is the form of disease without systemic abnormalities, and accounts for 70–80% of all RP patients. When RP is associated with other, non-ocular syndromes and systemic diseases, it is referred to as syndromic RP, which accounts for 20–30% of all RP patients.

3.2.3.1.8 The most common form of syndromic RP is Usher syndrome. Usher patients have congenital, or early-onset hearing impairment followed by development of RP. Bardet-Biedl syndrome is another common syndromic form in the Arabian Gulf and is associated with polydactyly, obesity, renal abnormalities, and developmental delay. However, partial phenotypes are possible, and this can be uncovered by genetic testing.

3.2.3.2 **Genetic causes and Inheritance Pattern:** [8,20,23,24,25]

3.2.3.2.1 Mutations in more than 60 genes are known to cause RP with different inheritance patterns (Table 1). Full list of genes causing RP and other inherited retinal disorders are included in Appendix 1.

3.2.3.2.2 The genes associated with RP play essential roles in the structure and function of photoreceptors in the retina. Mutations in any of the genes responsible for RP lead to a gradual loss of rods and cones in the retina.

3.2.3.2.3 The progressive degeneration of these cells causes the characteristic pattern of vision loss that occurs in people with RP. Rods typically break down before cones, which is why night vision impairment is usually the first sign of the disorder. Daytime vision is disrupted later, as both rods and cones are lost.

3.2.3.2.4 RP has different heritability patterns across different populations and can follow an autosomal recessive pattern. In global populations, these are responsible for about 20% of cases of RP. In the Middle East, autosomal recessive pattern is more common than autosomal dominant cases. Globally, the autosomal dominant inheritance pattern causes between 10–20% of cases of RP, while X-linked recessive inheritance causes 10%. The remaining approximately 50% of RP cases are isolated and have no previous family history and no known cause.

3.2.3.2.5 Mutations in the RHO gene are the leading cause of autosomal dominant retinitis pigmentosa reported globally, accounting for 20 to 30% of all cases.

3.2.3.2.6 In the Middle East, the most common genetic cause of RP is due to mutations in the *TULP1, RP1, IMPG2* genes.

3.2.3.2.7 At least 35 genes have been associated with the autosomal recessive form of the disorder. The most common gene variant reported globally is in the USH2A gene, with mutations in this gene responsible for 10% to 15% of all global cases of autosomal recessive retinitis pigmentosa.

3.2.3.2.8 Changes in at least 2 genes are thought to cause the X-linked form of the disorder. Pathogenic variants associated with X-linked RP affect predominately male individuals. Female carriers of a disease-causing variant sometimes can be affected clinically, and, in these cases, typically present with a milder phenotype than male patients. Mutations in the RPGR and RP2 genes account for most cases of X-linked RP.

Table 1: Genes and Inheritance Pattern of Retinitis Pigmentosa

Disease category	No. of identified genes
Autosomal dominant retinitis pigmentosa	22
Autosomal recessive retinitis pigmentosa	36
X-linked retinitis pigmentosa	2

3.2.3.3 **Genetic Testing:** [23,24,25]

3.2.3.3.1 Genetic testing can aid in attaining an accurate diagnosis which can be helpful in understanding which emerging treatment approaches and clinical trials might be appropriate. As treatment is available for *RPE65* causing RP, it is essential that genetic testing be offered for patients with RP when the phenotype is consistent with *RPE65* mutations. Genetic testing also can uncover other treatable forms of RP and risk for extraocular disease, allowing anticipatory management.

3.2.3.4 **Treatment and management:** [13,14,22,23,24,25,26,27,28]

3.2.3.4.1 Luxturna (voretigene neparvovec) is the first FDA approved therapy for RP and is only authorized for the treatment of a small sub-population of RP patients that have biallelic *RPE65* mutations and sufficient viable retinal cells. Further details regarding indication, dosage, and administration are included in Appendix 3.

3.2.3.4.2 Management is typically reliant on supportive care including vision aids and rehabilitation training programs to help RP affected individuals make the most of their vision. Multiple studies have demonstrated improvements in the quality of life in patients with visual impairment following low-vision rehabilitation services.

3.2.3.4.3 Appropriate optical, non-optical, or electronic prescriptions, and training, instruction, or therapies designed to enhance sight and improve efficiency offer some level or form of remediation. A low-vision aid (LVA) yields improvement in visual performance and can include corrective glasses; filtering lenses; optical and non-optical LVAs (e.g., magnifiers, telescopes, reading stands); electronic assistive technologies, such as closed-circuit television, screen readers; and, more recently, portable electronic devices.

3.2.4 Achromatopsia

3.2.4.1 **Overview:** [29,30]

3.2.4.1.1 Achromatopsia is a rare inherited retinal degeneration affecting all three types of cone photoreceptor cells that results in reduced visual acuity, photophobia, hemeralopia, and severe loss of color discrimination.

3.2.4.1.2 There are 2 types of achromatopsia, complete and incomplete. People with complete achromatopsia cannot perceive any colors; they see only black, white, and shades of gray. Incomplete achromatopsia is a milder form of the condition that allows some color discrimination.

3.2.4.1.3 Complete achromatopsia is more common than incomplete achromatopsia.

3.2.4.1.4 Achromatopsia is also characterized by other problems with vision, including photophobia, nystagmus, and low visual acuity. Affected individuals can also experience hyperopia or, less commonly, myopia.

3.2.4.1.5 These vision problems are congenital and manifest within the first few months of life.

3.2.4.2 **Genetic causes and Inheritance Pattern:** [29,30,31]

3.2.4.2.1 Achromatopsia results from changes in one of several genes: *CNGA3, CNGB3, GNAT2, PDE6C,* or *PDE6H*. [25,26]

3.2.4.2.2 Changes in these genes prevent cones within the retina, which are responsible for daylight vision, from reacting appropriately to light, which interferes with phototransduction.

3.2.4.2.3 In complete achromatopsia, cones are nonfunctional, and vision depends entirely on the activity of rods within the retina. This total loss of cone function leads to a total lack of color vision and causes other vision problems.

3.2.4.2.4 Individuals with incomplete achromatopsia retain some cone function and have limited color vision and their other vision problems tend to be less severe.

3.2.4.2.5 This condition is inherited in an autosomal recessive pattern.

3.2.4.3 **Treatment and management:** [29,30,31,32]

3.2.4.3.1 There are currently no approved treatment options for patients with achromatopsia. Tools are available to help patients manage

the symptoms of visual impairment, such as deep red tinted spectacles or contact lenses to reduce symptoms of light sensitivity, and magnifiers to deal with poor visual acuity. Underlying amblyopia can be managed with refractive correction. [25,27]

3.2.4.3.2 Genetic counseling is recommended for affected individuals and their families. Genetic counselors help individuals and families assess the chance of inherited disease as well as understand and adapt to its implications.

3.2.4.4 **Genetic testing:** [29,30,31,32]

3.2.4.4.1 Genetic testing can aid in attaining an accurate diagnosis which can be helpful in understanding which emerging treatment approaches and clinical trials might be appropriate. It also permits family planning and genetic counseling.

3.2.5 Stargardt disease

3.2.5.1 **Overview:** [33,34,35]

3.2.5.1.1 Stargardt macular degeneration is a genetic eye disorder that causes progressive vision loss.

3.2.5.1.2 This disorder affects a small area near the center of the retina called the macula. The macula is responsible for the type of vision needed for detailed tasks such as reading, driving, and recognizing faces.

3.2.5.1.3 In most people with Stargardt macular degeneration, a fatty yellow pigment called lipofuscin builds up in cells underlying the macula. Over time, the abnormal accumulation of this substance can damage cells that are critical for clear vision.

3.2.5.1.4 Stargardt macular degeneration patients can also have impaired color vision. People with advanced Stargardt macular degeneration that progresses to pan-retinal degeneration can have problems with night vision that can make it difficult to navigate in low light.

3.2.5.1.5 The signs and symptoms of Stargardt macular degeneration typically appear in late childhood to early adulthood and worsen over time.

3.2.5.1.6 In the UAE, a severe early childhood subtype has been identified due to a double mutant founder mutation.

3.2.5.2 **Genetic Causes and Inheritance Patterns:** [33,34,35,36]

3.2.5.2.1 Stargardt macular degeneration is caused by variants, most commonly in the *ABCA4* gene, and less often in the *ELOVL4* gene. *ABCA4* and *ELOVL4* genes are responsible for coding proteins that are found in photoreceptors in the retina.

3.2.5.2.2 The *ABCA4* gene affects how the body uses Vitamin A to make cells in the retina, as the ABCA4 protein transports toxic substances out of photoreceptors. Mutations in the *ABCA4* gene prevent the ABCA4 protein from removing toxic byproducts from photoreceptors causing toxic substances to build up and form lipofuscin in the photoreceptors and the surrounding cells of the retina, eventually causing cell death. Loss of cells in the retina causes the progressive vision loss associated with Stargardt disease.

3.2.5.2.3 The *ELOVL4* protein role lies in the making of long-chain fatty acids and is primarily found in the retina but is also expressed in the brain and skin. The function of very long-chain fatty acids within the retina is unknown. Mutations in the *ELOVL4* gene leads to the formation of ELOVL4 protein clumps that build up and may interfere with retinal cell functions, ultimately leading to cell death.

3.2.5.2.4 *ABCA4*-related Stargardt disease is autosomal recessive. *ELOVL4*-related Stargardt disease is autosomal dominant.

3.2.5.3 **Treatment and management:** [33,34,35,36]

3.2.5.3.1 Currently there is no available treatment for Stargardt disease, but low vision rehabilitation can reduce progression of the disease. Spectacles including prismatic glasses have been found to meet the need of the majority of patients with Stargardt's disease for reading.

3.2.5.3.2 Stargardt patients should be encouraged to maintain good sun protection, as exposure to bright light can lead to the formation of all-trans-retinal in photoreceptors and contribute to lipofuscin

accumulation.

3.2.5.3.3 Patients should avoid high doses of vitamin A, which can lead to increased accumulation of lipofuscin and worsening of disease. Smoking also worsens the disease.

3.2.5.3.4 Genetic counseling is recommended for affected individuals and their families. Genetic counselors help individuals and families assess the chance of inherited disease as well as understand and adapt to its implications.

3.2.5.4 **Genetic testing:**

3.2.5.4.1 Genetic testing is available to precisely diagnose the type of macular degeneration.

3.2.6 Cone-rod dystrophy (CRD)

3.2.6.1 Overview:[37,38]

3.2.6.1.1 CRD is a group of related inherited eye disorders that causes vision loss, which becomes more severe over time.

3.2.6.1.2 These disorders affect the retina, which is the layer of light-sensitive tissue at the back of the eye. In people with cone-rod dystrophy, vision loss occurs as the light-sensing cells of the retina gradually deteriorate.

3.2.6.1.3 The genes associated with cone-rod dystrophy play essential roles in the structure and function of photoreceptors in the retina. The retina contains two types of photoreceptors, rods and cones. Rods are needed for vision in low light, while cones provide vision in bright light, including color vision.

3.2.6.1.4 The first signs and symptoms of cone-rod dystrophy, which often occur in childhood, are usually decreased visual acuity and increased photophobia.

3.2.6.1.5 These features are typically followed by impaired color vision, blind spots in the center of the visual field, and peripheral vision loss.

3.2.6.1.6 Over time, affected individuals develop night blindness and a worsening of their peripheral vision, which can limit independent mobility.

3.2.6.1.7 Decreasing visual acuity makes reading increasingly difficult and most affected individuals are legally blind by mid-adulthood. As the condition progresses, individuals may develop involuntary eye movements.

3.2.6.2 Genetic Causes and Inheritance Pattern[8,37,38,39,40,41,42]

3.2.6.2.1 Mutations in more than 30 genes are known to cause CRD, which are distinguished by their genetic cause and their pattern of inheritance being either autosomal recessive, autosomal dominant, and X-linked recessive pattern. Full list of genes and their mode of inheritance are included in Appendix 4.

3.2.6.2.2 Approximately 20 of these genes are associated with the form of CRD that is inherited in an autosomal recessive pattern. Mutations in the *ABCA4* gene are the most common cause of autosomal recessive CRD reported globally, accounting for 30 to 60% of cases. Most of the *ABCA4* gene variants that cause cone-rod dystrophy change amino acids in the ABCA4 protein. The altered protein cannot remove N-retinylidene-PE from photoreceptors. As a result, N-retinylidene-PE combines with another substance to produce a molecule called N-retinylidene-N-retinylethanolamine (A2E), which builds up in these cells. The buildup of A2E is toxic to photoreceptors and leads to their deterioration, causing progressive vision loss in people with cone-rod dystrophy. Cone-rod dystrophy caused by *ABCA4* gene variants tends to be associated with more severe vision problems than cone-rod dystrophy caused by other genetic variants.

3.2.6.2.3 In the Middle East, mutations in the *TULP1* gene are the most common cause of CRD followed by mutations in the *KCNV2*, *ABCA4, IMPG2* genes.

3.2.6.2.4 At least 10 genes have been associated with CRD that is inherited in an autosomal dominant pattern. Mutations in the *GUCY2D* and *CRX* genes account for about half of these cases reported globally.

3.2.6.2.5 Changes in at least two genes cause the X-linked recessive form of

the disorder, which are rare.

3.2.6.3 **Treatment and management:** [38,39,42]

3.2.6.3.1 There is no cure for cone dystrophy but there are ongoing gene therapy clinical trials.

3.2.6.3.2 Treatment is currently directed toward the specific symptoms that are apparent in affected individuals. Treatment may include using tinted lenses or dark sunglasses in bright environments and magnifying devices to assist in reading and other similar activities.

3.2.6.3.3 Genetic counseling is recommended for affected individuals and their families. Genetic counselors help individuals and families assess the chance of inherited disease as well as understand and adapt to its implications.

3.2.7 Choroideremia

3.2.7.1 **Overview:** [43,44,45]

3.2.7.1.1 Choroideremia is a type of chorioretinal degeneration, also known as *CHM*-associated retinal degeneration.

3.2.7.1.2 This condition is characterized by progressive vision loss that mainly affects males.

3.2.7.1.3 The first symptom of this condition is usually night blindness, which can occur in early childhood.

3.2.7.1.4 A progressive narrowing of the field of vision follows, as well as a decrease in visual acuity.

3.2.7.1.5 These vision problems are due to atrophy of cells in the retina and choroid. The vision impairment worsens over time, but progression varies among affected individuals. However, all choroideremia patients' individuals will eventually develop blindness, most commonly in late adulthood.

3.2.7.2 **Genetic Causes and Inheritance Pattern:** [43,44,45]

3.2.7.2.1 Choroideremia is caused by mutations in the *CHM* gene which provides instructions for producing the Rab escort protein-1, REP-1. REP-1 attaches to molecules called Rab proteins within the cell and directs them to the organelles and are involved in intracellular trafficking.

3.2.7.2.2 Mutations in the *CHM* gene lead to an absence of REP-1 protein or the production of a REP-1 protein that cannot carry out its protein escort function. This lack of functional REP-1 prevents Rab proteins from reaching and binding to the organelle membranes. Without the aid of Rab proteins in intracellular trafficking, cells die prematurely.

3.2.7.2.3 REP-1 and another similar protein, REP-2, are expressed throughout the body. When REP-1 is absent or nonfunctional, REP-2 can perform the protein escort duties of REP-1 in many of the body's tissues. Very little REP-2 protein is present in the retina, however, so it cannot compensate for the loss of REP-1 in this instance.

3.2.7.2.4 Loss of REP-1 function and subsequent misplacement of Rab proteins within the cells of the retina causes the progressive vision loss characteristic of choroideremia.

3.2.7.2.5 Choroideremia is inherited in an X-linked recessive pattern. In males, who have only one X chromosome, one altered copy of the gene in each cell is sufficient to cause the condition. In females, who have two X chromosomes, a mutation must be present in both copies of the gene to cause the disorder. Males are affected by X-linked recessive disorders much more frequently than females.

3.2.7.3 **Treatment and Management:** [43,44,45,46,47]

3.2.7.3.1 Currently, there is no treatment or cure for choroideremia.

3.2.7.3.2 As choroideremia is caused by a mutation of one gene, it is a promising candidate for successful gene therapy. Research is ongoing, however more studies will be needed to investigate further clarify the effectiveness and safety of these therapies.

3.2.7.3.3 Genetic counseling is recommended for affected individuals and their families. Genetic counselors help individuals and families assess the chance of inherited disease as well as understand and adapt to its implications.

3.3 Genetic Testing

3.3.1 Gene Panel

3.3.1.1 For Emirati Genome Program participants, an inherited retinal disorder panel covering 329 genes associated with inherited retinal disorders is available (Table 2), detecting genes covered above. The panel is currently offered as part of clinical genomics panels within the Emirati Genome Program. Genetic testing for Emirati Genome Program participants is available through Biogenix Lab, M42.

3.3.1.2 Genetic testing is helpful in identifying if there is a genetic cause and providing patients with an accurate diagnosis. It can also identify risk for non-ocular disease.

3.3.1.3 Genetic testing can aid in understanding which emerging treatment and/or clinical trials are the most appropriate for patients.

Table 2: Inherited Retinal Disorder Genetic Testing Panel

ABCA4	*IFT43*	*RPE65*	*CLUAP1*	*PCARE*	*ABHD12*	*IFT80*	*RPGRIP1*	*CTNNA1*	*PRPF8*	*CLN3*
ADAM9	*IMPDH1*	*RTN4IP1*	*CNNM4*	*PDE6C*	*ADAMTSL4*	*IMPG2*	*SAMD11*	*DHX32*	*RBP1*	*CNGB1*
ADIPOR1	*IQCB1*	*SEMA4A*	*COL9A1*	*PEX1*	*AHI1*	*JAG1*	*SIX6*	*DTHD1*	*RDH11*	*COL18A1*
ALMS1	*KIAA0586*	*SLC45A2*	*CRX*	*PEX14*	*ARL13B*	*KIF11*	*SNRNP200*	*FAM161A*	*RGS9*	*CPLANE1*
ARL6	*KLHL7*	*TCTN1*	*CYP4V2*	*PEX3*	*ARSG*	*LRAT*	*TCTN3*	*FZD4*	*ROM1*	*CTSD*
ATOH7	*LRP2*	*TIMP3*	*DRAM2*	*PITPNM3*	*BBIP1*	*LYST*	*TMEM107*	*GNPTG*	*RPGRIP1L*	*DHX38*
BBS12	*MAPKAPK3*	*TMEM216*	*ELOVL4*	*POC5*	*BBS4*	*MFN2*	*TMEM237*	*GRM6*	*SCLT1*	*DYNC2I2*
BBS5	*MFRP*	*TMEM67*	*EXOSC2*	*PRCD*	*BBS9*	*MIR204*	*TPP1*	*HARS1*	*SLC24A1*	*FBLN5*
CA4	*MPDZ*	*TRIM32*	*FRMD7*	*PRPF4*	*CACNA1F*	*MTRFR*	*TRPM1*	*IDH3A*	*SPATA7*	*GDF6*
CC2D2A	*NAGLU*	*TTC8*	*GNAT2ss*	*RAB28*	*CDH23*	*NDP*	*TTPA*	*IFT81*	*TEAD1*	*GNS*
CEP164	*NMNAT1*	*TUBGCP6*	*GPR179*	*RCBTB1*	*CEP250*	*NPHP3*	*TYR*	*INPP5E*	*TMEM126A*	*GRN*
CEP78	*NR2F1*	*USH1C*	*GUCA1B*	*REEP6*	*CERKL*	*NYX*	*USH2A*	*KCNJ13*	*TRAF3IP1*	*HGSNAT*
CHM	*OFD1*	*WDPCP*	*HMCN1*	*RIMS1*	*CISD2*	*OPA3*	*WFS1*	*KIF7*	*TSPAN12*	*IDH3B*
CLN5	*OTX2*	*ZNF423*	*IFT172*	*RP2*	*CLN8*	*PAX2*	*ACBD5*	*LRIT3*	*TUB*	*IFT88*
CLRN1	*PAX6*	*ABCC6*	*IFT74*	*RPGR*	*CNGA1*	*PCDH15*	*ADGRA3*	*LZTFL1*	*TYRP1*	*INVS*
CNGB3	*PDE6B*	*ADAMTS18*	*IMPG1*	*SAG*	*COL11A1*	*PDE6D*	*AHR*	*MKKS*	*VCAN*	*KCNV2*
COL2A1	*PDZD7*	*AGBL5*	*ITM2B*	*SGSH*	*COL9A2*	*PEX10*	*ARL2BP*	*MTTP*	*WHRN*	*KIZ*
CRB1	*PEX13*	*ARHGEF18*	*KIAA1549*	*SLC7A14*	*CSPP1*	*PEX16*	*ASRGL1*	*NEK2*	*ACO2*	*LRMDA*
CWC27	*PEX26*	*ARMC9*	*LCA5*	*TCTN2*	*DHDDS*	*PEX5*	*BBS1*	*NPHP4*	*ADGRV1*	*MAK*

DNAJC17	*PHYH*	*B9D1*	*LRP5*	*TMED7*	*DSCAML1*	*PLA2G5*	*BEST1*	*OAT*	*AIPL1*	*MKS1*
EFEMP1	*POC1B*	*BBS2*	*MERTK*	*TMEM231*	*EMC1*	*POMGNT1*	*CACNA2D4*	*OPN1SW*	*ARL3*	*MYO7A*
ERCC6	*PPT1*	*BBS7*	*MFSD8*	*TOPORS*	*EYS*	*PRDM13*	*CDH3*	*PCYT1A*	*ATF6*	*NEUROD1*
FLVCR1	*PRPF31*	*CABP4*	*MTPAP*	*TRNT1*	*FSCN2*	*PRPF6*	*CEP290*	*PDE6G*	*BBS10*	*NR2E3*
GNAT1	*PRPS1*	*CCT2*	*NBAS*	*TTLL5*	*GNB3*	*RAX2*	*CFAP410*	*PEX11B*	*C1QTNF5*	*OCA2*
GPR143	*RBP4*	*CEP19*	*NPHP1*	*TULP1*	*GPR45*	*RD3*	*CLCC1*	*PEX19*	*CAPN5*	*OR2W3*
GUCA1A	*RDH5*	*CEP83*	*NRL*	*USH1G*	*GUCY2D*	*RGR*	*CNGA3*	*PEX6*	*CDHR1*	*PDE6A*
HK1	*RHO*	*CIB2*	*OPA1*	*WDR19*	*HMX1*	*RLBP1*	*COL11A2*	*PLK4*	*CEP41*	*PDE6H*
IFT140	*RP1L1*	*CLN6*	*P3H2*	*ZNF513*	*IFT27*	*RP9*	*COL9A3*	*PROM1*	*CFAP418*	*PEX12*
PEX2	*PEX7*	*PNPLA6*	*PRPF3*	*PRPH2*	*RBP3*	*RDH12*	*RGS9BP*	*RP1*	*RS1*	*SDCCAG8*
SPP2	*TIMM8A*	*TMEM138*	*TREX1*	*TTC21B*	*TUBGCP4*	*UNC119*	*VPS13B*	*ZNF408*	*SLC24A5*	

3.3.2 **Genetic Testing Workflow**

3.3.2.1 All requests for the inherited retinal disorder panel should meet patient criteria for testing and be sent to an accredited laboratory to perform genetic testing with all required laboratory request forms and consent forms found in Appendix 5. Genetic testing is appropriate for patients with a clinically-suspected genetic retinal degeneration. Genetic counseling must be conducted to ensure patients understand their genetic findings, available treatments, and the implications for any future family planning.

3.3.2.2 At risk family members can also benefit from genetic testing, although the implications of genetic testing for asymptomatic individuals in the absence of established therapies must be considered and must be accompanied by genetic counseling.

3.3.2.3 For coverage of genetic testing, patients must be Emirati Genome Program participants and Thiqa holders.

3.3.2.4 The workflow for sending samples for Emirati Genome Program participants to Biogenix Lab (M42) is illustrated in Figure 2.

3.3.2.5 Familial cascade testing is important in cases where pathogenic or likely pathogenic variants have been identified. For autosomal or X-linked conditions, screening of both parents or mothers respectively, is recommended to prevent recurrence. Workflow for familial cascade testing is highlighted in Figure 3.

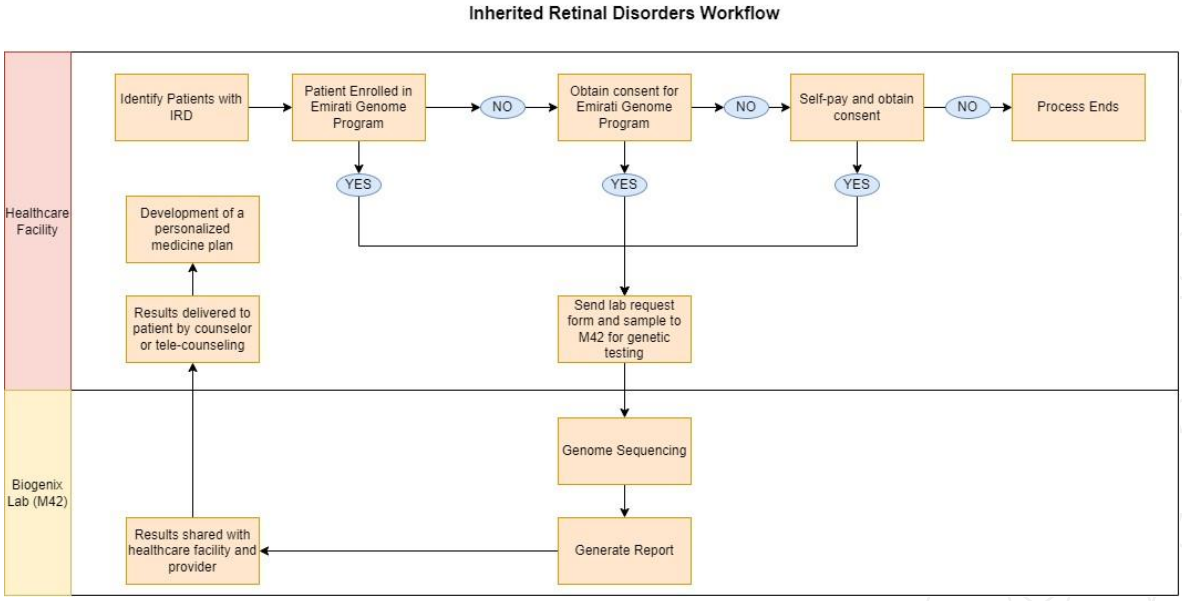

Figure 2: Inherited Retinal Disorders Workflow

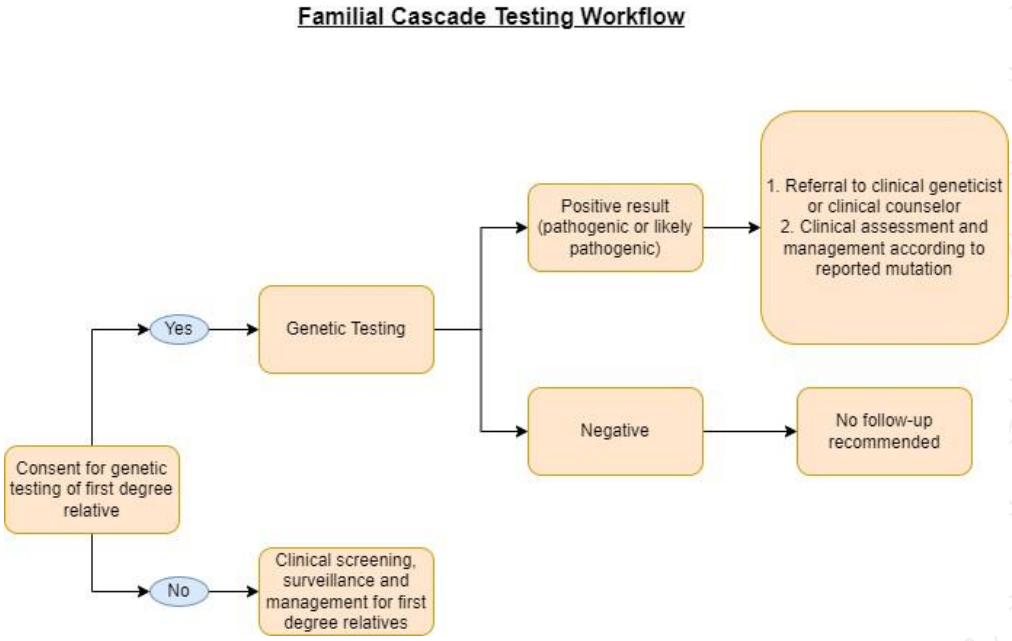

Figure 3: Familial Cascade Testing Workflow

4.Relevant References Documents			
No.	**Reference Date**	**Reference Name**	**Relation Explanation / Coding / Publication Links**
1	2022	Guidelines on Clinical Assessment of Patients with Inherited Retinal Degenerations	https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with
2	2024	Lions Eye Institute: Inherited Retinal Disease	https://www.lei.org.au/services/eye-health-information/inherited-retinal-disease/
3	2023	WebMD: Inherited Retinal Dystrophy	https://www.webmd.com/eye-health/features/genetics-inherited-retinal-dystrophy
4	2024	Retina International: IRDs	https://retina-international.org/irds/
5	2022	Genome Medicine: A guide for the diagnosis of rare and undiagnosed disease: beyond the exome	https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-022-01026-w
6	2021	Orphanet Journal of Rare Diseases:Genetic testing and diagnosis of inherited retinal diseases	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8670140/
7	2014	American Academy of Ophthalmology: Recommendations for Genetic Testing of Inherited Eye Diseases	https://www.aao.org/education/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d
8	2023	BMC Medical Genomics: The genetic landscape of inherited retinal dystrophies in Arabs	https://pubmed.ncbi.nlm.nih.gov/37127645/
9	2022	MedicineNet: How Many Inherited Retinal Diseases Are There?	https://www.medicinenet.com/how_many_inherited_retinal_diseases_are_there/article.htm
10	2024	Boston Childrens Hospital: Inherited Retinal Disorders	https://www.childrenshospital.org/conditions/inherited-retinal-disorders
11	2014	British Journal of	https://pubmed.ncbi.nlm.nih.gov/24997176/

12	2022	MedlinePlus Genetics: Leber congenital amaurosis	https://medlineplus.gov/genetics/condition/leber-congenital-amaurosis/
13	2024	European Medicines Agency: Luxturna	https://www.ema.europa.eu/en/medicines/human/EPAR/luxturna
14	2022	U.S Food and Drug Administration: Luxturna	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna
15	2023	National Eye Institute: Retinitis Pigmentosa	https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinitis-pigmentosa
16	2022	Journal of Clinical Ophthalmology: Retinitis Pigmentosa: Burden of Disease and Current Unmet Needs	https://pubmed.ncbi.nlm.nih.gov/35757022/
17	2024	American Academy of Ophthalmology: What is Retinitis Pigmentosa	https://www.aao.org/eye-health/diseases/what-is-retinitis-pigmentosa
18	2022	UpToDate: Retinitis pigmentosa: Clinical presentation and diagnosis	https://pro.uptodatefree.ir/Show/6905
19	2003	Developments in Ophthalmology: Bardet-Biedl syndrome and Usher syndrome	https://pubmed.ncbi.nlm.nih.gov/12876834/
20	2024	Retinitis Pigmentosa	https://www.ncbi.nlm.nih.gov/books/NBK519518/
21	2024	Opthalmic Genetics: Usher syndrome in the United Arab Emirates	https://pubmed.ncbi.nlm.nih.gov/39016003/
22	2024	Diabetes, Obesity, and Metabolisn	https://dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.15494?af=R
23	2010	MedlinePlus Genetics: Retinitis Pigmentosa	https://medlineplus.gov/genetics/condition/retinitis-pigmentosa/
24	2011	Current Genomics: Retinitis Pigmentosa: Genes and Disease Mechanisms	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131731/pdf/CG-12-238.pdf

25	2017	3 Biotech: Genetic characterization and disease mechanism of retinitis pigmentosa; current scenario	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5515732/#CR7
26	2020	Cochrane Database System Review: Low vision rehabilitation for better quality of life in visually impaired adults	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6984642/
27	2007	American Optometric Association: Care of the Patient with	https://www.aao.org/education/low-vision-and-vision-rehab
28	2016	Visual Impairment (Low Vision Rehabilitation)	https://retinalphysician.com/issues/2016/novdec/emerging-treatments-for-achromatopsia/#ref25
28	2019	Disability and Rehabilitation: Factors related to the use of magnifying low vision aids: a scoping review	https://pubmed.ncbi.nlm.nih.gov/31120308/
29	2024	American Academy of Ophthalmology: Achromatopsia	https://eyewiki.aao.org/Achromatopsia
30	2015	MedlinePlus Genetics: Achromatopsia	https://medlineplus.gov/genetics/condition/achromatopsia/
31	2024	Retina: The genetic basis of clinically-suspected achromatopsia in the United Arab Emirates	https://pubmed.ncbi.nlm.nih.gov/39024658/
31	2016	Retinal Physician: Emerging Treatments for Achromatopsia	https://retinalphysician.com/issues/2016/novdec/emerging-treatments-for-achromatopsia/#ref25
32	2021	National Eye Institute: Stargardt Disease	https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/stargardt-disease
33	2023	MedlinePlus Genetics: Stargardt macular degeneration	https://medlineplus.gov/genetics/condition/stargardt-macular-degeneration/

34	2008	Journal of College and Physicians: Visual Rehabilitation of Patients with Stargardt's Disease	https://www.jcpsp.pk/archive/2008/May2008/09.pdf
35	2014	American Academy of Ophthalmology: Diagnosis and Management of Stargardt Disease	https://www.aao.org/eyenet/article/diagnosis-management-of-stargardt-disease
36	2018	MedlinePlus Genetics: Cone-rod Dystrophy	https://medlineplus.gov/genetics/condition/cone-rod-dystrophy/
37	2019	British Journal of Ophthalmology: Progressive cone and cone-rod dystrophies: clinical features, molecular genetics and prospects for therapy	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6709772/
38	2009	The American Journal of Human Genetics: Mutations in CNNM4 Cause Recessive Cone-Rod Dystrophy with Amelogenesis Imperfecta	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668018/pdf/main.pdf
39	2024	Gene Cards: The Human Gene Database	https://www.genecards.org/
40	2024	An Online Catalog of Human Genes and Genetic Disorders (OMIM)	https://www.omim.org/
41	2021	National Organization for Rare Diseases: Cone Dystrophy	https://rarediseases.org/rare-diseases/cone-dystrophy/
42	2020	Retina: Phenotype-Guided Genetic Testing of Pediatric Inherited Retinal Disease in the United Arab Emirates	

42	2003	GeneReviews: Choroideremia	https://www.ncbi.nlm.nih.gov/books/NBK1337/
43	2024	American Academy of Ophthalmology: Choroideremia	https://eyewiki.aao.org/Choroideremia
44	2013	MedlinePlus Genetics :Choroideremia	https://medlineplus.gov/genetics/condition/choroideremia/#:~:text=The%20first%20symptom%20of%20this,see%20details%20(visual%20acuity).
45	2021	Medicina: Update on Gene Therapy Clinical Trials for Choroideremia and Potential Experimental Therapies	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7826687/
46	2019	Clinical Ophthalmology: Choroideremia: Update On Clinical Features And Emerging Treatments	https://pmc.ncbi.nlm.nih.gov/articles/PMC6874149/
47	2022	American Academy of Ophthalmology: Guidelines on Clinical Assessment of Patients with Inherited Retinal Degenerations	https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with
48	2021	Novartis: Luxturna	https://www.novartis.com/sg-en/sites/novartis_sg/files/Luxturna-Oct2021.SINv1-app190423-pdf.pdf

5. Appendices

No.	Appendix Name
1	Genes that when mutated are associated with Inherited Retinal Disorders
2	Clinical Evaluation: Inherited Retinal Degenerative Diseases
3	Indication and Dosage Requirements for Luxturna
4	Genes that when mutated are associated with Cone-rod dystrophy
5	Consent form for Emirati Genome Participants

Appendix 1: Genes that when mutated are associated with Inherited Retinal Disorders [243,24,25,41]

Table 3: Genes that when mutated are associated with Inherited Retinal Disorders

Identified gene	Function of gene	Other phenotypes	Inheritance
BEST1	Provides instructions for making Bestrophin	Recessive retinitis Pigmentosa	Autosomal Dominant/Autosomal Recessive
DHX38	Embryogenesis, spermatogenesis, and cellular growth and division	Early onset with macular coloboma	Autosomal Dominant/Autosomal Recessive
KIZ	Required for stabilizing the expanded pericentriolar material around the centriole	None	Autosomal Dominant/Autosomal Recessive
NR2E3	Rod development and repressor of cone development	Recessive retinitis pigmentosa	Autosomal Dominant/Autosomal Recessive
NRL	Transcription factor which regulates the expression of RHO and PDE6B genes	Autosomal recessive retinitis pigmentosa	Autosomal Dominant/Autosomal Recessive
RHO	Required for photoreceptor cell viability after birth	Recessive retinitis pigmentosa	Autosomal Dominant/Autosomal Recessive

RP1	Required for the differentiation of photoreceptor cells	Recessive retinitis pigmentosa	Autosomal Dominant/Autosomal Recessive
RPE65	Retinal metabolism	Recessive leber congenital amaurosis	Autosomal Dominant/Autosomal Recessive
ABCA4	Retinal metabolism	Recessive macular dystrophy Cone-rod dystrophy	Autosomal Recessive
ADIPOR1	Receptor for ADIPOQ, required for normal glucose and fat homeostasis	Bardet-Biedl like	Autosomal Recessive
ARL2BP	Role in the nuclear translocation	None	Autosomal Recessive
C2orf71	Might have an important role in developing of normal vision	None	Autosomal Recessive
C8Oorf37	Unknown	None	Autosomal Recessive
CA4	Involves in respiration, calcification, acid–base balance	None	Autosomal Dominant
CERKL	Tissue maintenance and development	None	Autosomal Recessive
CLRN1	Conjugation	None	Autosomal Recessive
CNGA1	Phototransduction	None	Autosomal Recessive
CNGB1	Phototransduction	None	Autosomal Recessive
CRB1	Tissue maintenance and development	Recessive leber congenital amaurosis	Autosomal Recessive
CRX	Maintain normal rod and cone function	Dominant Leber congenital amaurosis	Autosomal Dominant
DHDDS	Catalysis	None	Autosomal Recessive
EMC1	Unknown	None	Autosomal Recessive
EYS	Protein of the extracellular matrix	Unknown	Autosomal Recessive
FAM161A	Unknown	Unknown	Autosomal Recessive
FSCN2	Acts as an actin bundling protein	None	Autosomal Dominant
GPR125	Orphan receptor	None	Autosomal Recessive
GUCA1B	Stimulates guanylyl cyclase 1 and guanylyl cyclase 2	Dominant macular dystrophy	Autosomal Dominant

HGSNAT	Participates in glycosaminoglycan degradation and glycan structures degradation	Recessive mucopolysaccharidosis	Autosomal Recessive
HK1	Helps in glycolysis and gluconeogenesis, energy pathway	Excessive nonspherocytic hemolytic anemia, recessive hereditary neuropathy (Russe)	Autosomal Dominant
IDH3B	Involved in Krebs cycle	Unknown	Autosomal Recessive
IFT140	Component of the IFT complex A, important role in proper development and function of ciliated cells and maintenance of ciliogenesis and cilia	Recessive Mainzer-Saldino syndrome, recessive Leber congenital amaurosis	Autosomal Recessive
IFT172	Necessary for cilia maintenance and formation. Plays an indirect role in hedgehog signaling	Recessive Bardet-Biedl syndrome	Autosomal Recessive
IMPDH1	Catalyzes the conversion of inosine 5’-phosphate (IMP) to xanthosine 5’-phosphate	Dominant Leber congenital amaurosis	Autosomal Dominant
IMPG2	Component of the retinal intercellular matrix	Unknown	Autosomal Recessive
KIAA1549	Unknown	None	Autosomal Recessive
KLHL7	mediates’Lys-48'-linked ubiquitination	None	Autosomal Dominant
LRAT	Retinal metabolism	Recessive leber congenital amaurosis	Autosomal Recessive
MAK	An important function in spermatogenesis	None	Autosomal Recessive
MERTK	Transmembrane protein	None	Autosomal Recessive
MVK	Regulatory site in cholesterol biosynthetic pathway	None	Autosomal Recessive
NEK2	Involves in control of centrosome separation and bipolar spindle formation	None	Autosomal Recessive
NEUROD1	Neurogenesis regulator D1, acts as a transcriptional activator	None	Autosomal Recessive
OR2W3	Initiate a neuronal response that triggers the perception of a smell	None	Autosomal Dominant
PDE6A	Phototransduction	None	Autosomal Recessive

PDE6B	Phototransduction	Dominant congenital stationary night blindness	Autosomal Recessive
PDE6G	Phototransduction	None	Autosomal Recessive
POMGNT1	Participates in O-mannosyl glycosylation	None	Autosomal Recessive
PRCD	Unknown	Unknown	Autosomal Recessive
PROM1	Cellular structure	Recessive retinitis pigmentosa with macular degeneration	Autosomal Recessive
PRPF3	Participates in pre-mRNA splicing	None	Autosomal Dominant
PRPF31	Involved in pre-mRNA splicing	None	Autosomal Dominant
PRPF4	Participates in pre-mRNA splicing	None	Autosomal Dominant
PRPF6	Participates in pre-mRNA splicing	None	Autosomal Dominant
PRPF8	Functions as a scaffold that mediates the ordered assembly of spliceosomal proteins and snRNAs	None	Autosomal Dominant
PRPH2	Essential for disk morphogenesis	Digenic forms with *ROM1*	Autosomal Dominant
RBP3	Retinal metabolism	Unknown	Autosomal Recessive
RDH11	Shows an oxidoreductive catalytic activity for retinoids, involves in the metabolism of short-chain aldehydes	None	Autosomal Recessive
RDH12	Key enzyme in the formation of 11-cis-retinal from 11-cis-retinol during regeneration of the cone visual pigments	Recessive Leber congenital amaurosis	Autosomal Dominant
RGR	Retinal metabolism	Dominant choroidal sclerosis	Autosomal Recessive
RLBP1	Retinal metabolism	Recessive Bothnia dystrophy	Autosomal Recessive
ROM1	Essential for disk morphogenesis	Digenic retinitis pigmentosa with *PRPH2*	Autosomal Dominant
RP2	Involved in beta-tubulin folding	None	X-Linked
RP9	Roles in B-cell proliferation in association with PIM1	None	Autosomal Dominant
RPGR	Intraflagellar transport	X-linked cone dystrophy, X-linked congenital stationary night blindness	X-Linked
SAG	Phototransduction	Recessive Oguchi disease	Autosomal Recessive

SEMA4A	Cell surface receptor	Dominant cone-rod dystrophy	Autosomal Dominant
SLC7A14		None	Autosomal Recessive
SNRNP200	Involves in spliceosome assembly, activation and disassembly	None	Autosomal Dominant
SPATA7	Unknown	None	Autosomal Recessive
SPP2	It could coordinate an aspect of bone turnover	None	Autosomal Dominant
TOPORS	It has the ability to interact with the tumor suppressor protein P53	None	Autosomal Dominant
TTC8	Cellular structure	Recessive Bardet-Biedl syndrome	Autosomal Recessive
TULP1	Tissue maintenance and development	Recessive Leber congenital amaurosis	Autosomal Recessive
USH2A	Cellular structure	Recessive Usher syndrome	Autosomal Recessive
ZNF408	May be involved in transcriptional regulation	Dominant familial exudative vitreoretinopathy	Autosomal Recessive
ZNF513	Expression factor	None	Autosomal Recessive

Appendix 2. Clinical Evaluation: Inherited Retinal Degenerative Disease

The following guideline is adapted from American Academy of Ophthalmology [48]

Table 4: Clinical Evaluation Guideline

Assessment	**Initial Visit**	**Follow Up Visit Every 1-2 Years**
History • Ocular (including current needs) • Medical (including current medications and history of retinotoxic medication use) • Family history of vision problems	1-4a	1-4
Pedigree	1-4	1-4
Clinical eye examination • Best corrected visual acuity: Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol (or equivalent) • Color vision testing (optional) • Slit lamp biomicroscopy • Intraocular pressure • Indirect ophthalmoscopy	1-4	1-4
Imaging • Color fundus photos* • Spectral Domain Optical Coherence Tomography • Fundus autofluorescence: Short wavelength with reduced illumination when possible • Infrared Reflectance or autofluorescence (when available)	1-4 1-4 1-4 1,3, 4	1-4 1-4 1, 3, 4
Visual fields • Kinetic • Static • Microperimetry	1-4 1-3b 1-4b	1-4 1-3b 1-4b
Electroretinography • Full-field ERGc (when appropriate) • Multifocal ERGd (when appropriate) • FST (useful with unsteady fixation or when ERG is non recordable)	1-4 2, 4	1-3 2, 4

Genetic Diagnostic Testing • Inherited Retinal Disorder Panel-329 Genes	1-4	1-4 (if earlier visits did not provide conclusive results)

Legend:

a) Numbers refer to clinical phenotypes:

1. Rod-cone degenerations, such as retinitis pigmentosa. Those with stationary rod-cone dysfunction, such as congenital stationary night blindness, should be evaluated similarly at baseline, then followed with clinical eye examinations only.
2. CRD. Conditions affecting cones that are traditionally considered stationary, such as achromatopsia, should also be evaluated similarly at baseline, then followed with eye examinations annually, as some cases may progress slowly, warranting ongoing follow up.
3. Chorioretinal degeneration degenerations, such as *CHM*-associated retinal degeneration (choroideremia) and gyrate atrophy.
4. Inherited dystrophies that involve the macula, such as cone degeneration, X-linked retinoschisis, *ABCA4*-associated macular degeneration (Stargardt disease), and *PRPH2*-associated macular degeneration (pattern dystrophy).

b) Static perimetry and microperimetry are of uncertain value for patients with advanced disease as they may have unstable, eccentric fixation that makes interpretation difficult.

c) Full-field ERG is not necessary in Best disease, North Carolina macular dystrophy, or in cases of pattern dystrophy limited to the macula. However, if electro-oculogram testing is not available, full-field ERG should be normal in Best disease. A full-field ERG is appropriate for a patient with macular changes for whom one is considering cone or cone-rod dystrophy in the differential diagnosis. Also, a non-detectable ERG is not recommended to be repeated.

d) Multifocal ERG is of uncertain value in patients when central acuity is significantly reduced or fixation is unstable, as mentioned above.

Appendix 3: Indication and Dosage Requirements for Luxturna (VORETIGENE NEPARVOVEC 0.05mg) [13,14,48]

1. Indications

Luxturna is indicated for the treatment of adult and pediatric patients with inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells as determined by the treating physician(s). Disease-causing biallelic RPE65 mutations should be confirmed by an accredited laboratory using validated assay methods

2. Dosage regimen

- Treatment should be initiated and administered by a retinal surgeon experienced in performing macular surgery.
- Patients will receive a single dose of 1.5 x 1011 vg of Luxturna in each eye. Each dose will be delivered into the subretinal space in a total volume of 0.3 mL. The individual administration procedure to each eye is performed on separate days within a close interval, but no fewer than 6 days apart.

3. Immunomodulatory regimen

Prior to initiation of the immunomodulatory regimen and prior to administration of Luxturna, the patient must be checked for symptoms of active infectious disease of any nature, and in case of such infection the start of treatment must be postponed until after the patient has recovered. Starting 3 days prior to the administration of Luxturna to the first eye, it is recommended that an immunomodulatory regimen is initiated following the schedule outlined in Table 4-1. Initiation of the immunomodulatory regimen for the second eye should follow the same schedule and supersede completion of the immunomodulatory regimen of the first eye.

Table 5: Pre- and post-operative immunomodulatory regimen

Pre-Operative	3 days prior to administration	Prednisone (or equivalent) 1mg/kg/day (maximum of 40 mg/day)
Post-Operative	4 days (including the day of administration)	Prednisone (or equivalent) 1mg/kg/day (maximum of 40 mg/day)
	Followed by 5 days	Prednisone (or equivalent) 0.5mg/kg/day (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day	Prednisone (or equivalent) 0.5mg/kg/day (maximum of 20 mg/day)

4. Special populations

4.1 Hepatic or renal impairment

The safety and efficacy of Luxturna have not been established in patients with hepatic or renal impairment. No dose adjustment is necessary in these patients.

4.2 Pediatric patients (below 18 years)

The safety and efficacy of Luxturna in children below 4 years of age have not been established. Treatment with Luxturna is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and Luxturna would potentially be diluted or lost during cell proliferation. No dose adjustment is necessary for pediatric patients aged 4 years and above.

4.3 Geriatric patients (65 years or above)

The safety and efficacy of Luxturna in patients 65 years or above have not been established. Clinical studies of Luxturna for this indication did not include patients aged 65 years and over.

5. Administration
5.1 Subretinal Preparation

Prepare voretigene neparvovex-rzyl within 4 hr of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC)

6. Dilution

- Thaw 1 single-dose vial of voretigene neparvovex-rzyl and 2 vials of diluent at room temperature
- Mix thawed diluent vials by gently inverting them ~5 times
- Visually inspect diluent and voretigene neparvovex-rzyl single-dose vials for particulates, cloudiness, or discoloration; do not use the vial(s) if particulates are present; new vial(s) of diluent should be used
- Using the 3-mL syringe with 20G 1-inch needle, transfer 2.7 mL of diluent to 10-mL glass vial
- Mix contents of thawed voretigene neparvovex-rzyl single-dose vial by gently inverting ~5 times
- Draw 0.3 mL voretigene neparvovex-rzyl into a 1-mL sterile syringe with a 27G ½-inch sterile needle
- Transfer 0.3 mL of voretigene neparvovex-rzyl to glass vial containing 2.7 mL of diluent
- Gently invert the 10-mL glass vial approximately 5 time to mix contents
- Label the 10-mL glass vial containing the diluted voretigene neparvovex-rzyl as follows: 'Diluted LUXTURNA'

7. Preparation

- To keep the syringes sterile, 2 operators are required for transfer of the contents of the 10-mL glass vial labeled 'Diluted LUXTURNA' into each of 2 sterile 1-mL syringes
- Primary operator withdraws 0.8 mL of the diluted voretigene neparvovex-rzyl into a sterile 1-mL syringe using a 27G ½-inch sterile needle while the secondary operator holds the 10-mL glass vial
- Prepare a total of two administration syringes
- Label the first syringe "Diluted LUXTURNA" and label the second syringe "Backup Diluted LUXTURNA" using the sterile skin marker
- The second syringe serves as a backup for the surgeon performing the subretinal administration procedure
- Discard the backup syringe after surgery if not used
- Visually inspect both syringes; if particulates, cloudiness, or discoloration are visible, do not use the syringe
- Place the syringes into the sterile plastic bag after visual inspection and seal the bag
- Place the sterile plastic bag with syringes containing diluted voretigene neparvovex-rzyl into an appropriate secondary container (eg, hard plastic cooler) for delivery to the surgical suite at room temperature

8. Subretinal Administration

For subretinal injection only

Items are required for administration

- Syringe containing diluted voretigene neparvovex-rzyl
- Subretinal injection cannula with a polyamide micro tip with an inner diameter of 41G
- Extension tube made of polyvinyl chloride <6 inch (15.2 cm) in length and with an inner diameter <1.4 mm

9. Subretinal injection

- Dilate eye and give adequate anesthesia to the patient
- Administer a topical broad-spectrum microbiocide to the conjunctiva, cornea, and eyelids prior to surgery
- Visually inspect voretigene neparvovex-rzyl prior to administration; if particulates, cloudiness, or discoloration are visible, do not use the product
- Connect the syringe containing the diluted voretigene neparvovex-rzyl to the extension tube and subretinal injection cannula
- Avoid excess priming volume; extension tube should not exceed 15.2 cm in length and 1.4 mm in inner diameter
- Inject drug slowly through extension tube and subretinal injection cannula to eliminate any air bubbles
- Confirm the volume of product available in the syringe for injection by aligning the plunger tip with the line that marks 0.3 mL
- After completing a vitrectomy, identify the intended site of administration (see prescribing information for further illustrated information)
- Recommended site of injection: Along the superior vascular arcade, >2 mm distal to the center of the fovea, avoiding direct contact with the retinal vasculature or with areas of pathologic features, such as dense atrophy or intraretinal pigment migration
- Inject drug slowly until an initial subretinal bleb is observed; then inject remaining volume slowly until the total 0.3 mL is delivered
- After completing the injection, remove subretinal injection cannula from the eye
- Following injection, discard all unused product
- Perform a fluid-air exchange, carefully avoiding fluid drainage near the retinotomy created for the subretinal injection
- Initiate supine head positioning immediately in the postoperative period
- Upon discharge, advise patients to rest in a supine position as much as possible for 24 hr

10. Storage

Drug and diluent: Store frozen at ≤-65°C

Following thaw of vials: Store at room temperature; further dilute and administer within 4 hr

Diluted drug: Store at room temperature just prior to injection procedure

Appendix 4: Genes that when mutated are associated with Cone-rod dystrophy [37,38,39,40,41,42]

Table 6: Genes that when mutated are associated with Cone-Rod Dystrophy

Gene	Potential Function	Inheritance
ABCA4	Retinoid cycle	Autosomal Recessive
CACNA1F	Neurotransmitter release	X linked
CNGA3	Phototransduction	Autosomal recessive
CNGB3	Phototransduction	Autosomal recessive
CRB1	Photoreceptor morphogenesis	autosomal recessive
CRX	Tissue development	Autosomal dominant
GUCY2D	Photoreceptor recovery	Autosomal dominant
PDE6C	Phototransduction	Autosomal recessive
PRPH2	Outer segment morphogenesis	Autosomal dominant
RPGR	Intraflagellar transport	X linked
ADAM9	Outer segment–RPE junction	Autosomal recessive
AIPL1	Tissue development	Autosomal dominant
CACNA2D4	Neurotransmitter release	Autosomal recessive
CDHR1	Outer segment morphogenesis	Autosomal recessive
CERKL	Photoreceptor survival	Autosomal recessive
CFAP410	Ciliogenesis	Autosomal recessive
CFAP418	photoreceptor outer segment disk morphogenesis	Autosomal recessive
CNNM4	metal ion transport	Autosomal recessive
DRAM2	Autophagy	Autosomal recessive
EYS	Unknown	autosomal recessive
GUCA1A	Photoreceptor recovery	Autosomal dominant
KCNV2	modulator	Autosomal recessive
PITPNM3	Tyrosine kinase signaling	Autosomal dominant
POC1B	Intraflagellar transport	Autosomal recessive
PROM1	Outer segment morphogenesis	Autosomal dominant
RAB28	Intraflagellar transport	Autosomal recessive
RAX2	Tissue development	Autosomal dominant
RIMS1	Neurotransmitter release	Autosomal dominant
RPGRIP1	Intracellular trafficking	Autosomal recessive
SEMA4A	Tissue development	Autosomal recessive
TTLL5	Steroid receptor signaling	Autosomal recessive
TULP1	Photoreceptor function and recovery	Autosomal recessive
UNC119	Neurotransmitter release	Autosomal dominant

Appendix 5: Consent form for Emirati Genome Participants

CONFIDENTIAL

CONSENT FORM
(Clinical Genomics)

BIOGENIX LABS

SECTION I: CONSENT FORM FOR CLINICAL GENETIC TESTING

To be filled in by the referring clinician (wherever applicable)

Name of individual to be tested:	
Name of legal guardian:	
Person to be contacted for results:	Name: Mobile No.: Email ID: Emirate's ID:
Name of test	
For Emirati only (mandatory answer please) Do you agree to participate to Emirati Genome program? In case of agreement, please sign the related consent	☐ Agree ☐ Disagree

G42 LABORATORY LLC, operating as Biogenix Laboratory, require a signed consent from the patient (or legal guardian, in case of minor or people of determination) prior to conducting a genetic analysis. Genetic testing will look into 'changes' (known as 'mutations') within your genetic material (called the DNA). Each genetic testing has its own indications and limitations. Because of the complexity of genetic testing and the important implications of the test results, results are reported by the Clinical Geneticist at Biogenix Laboratory. We highly recommend post-test genetic counselling for test results.

Declaration of consent

- I confirm that risks, benefits, and limitations of such genetic tests have been explained by a healthcare professional or genetic specialist before signing this form.
- I agree I can send my inquiries or concerns regarding my test to Biogenix Laboratory at clinical.genomics.testing@g42.ai.
- I confirm I have provided accurate information to the best of my knowledge and abilities as I understand that the accuracy of my results depends on providing the correct family relationship and clinical history of the disease.
- I consent to the collection by you of the personal data about me for the purposes of genetic testing (in each case insofar as provided): the personal details provided by me or my legal guardian in the in the Test Requisition Form (TRF)
- I understand that (i) my samples will be 'de-identified' before undergoing laboratory analysis, which is where my personal identifiable information is removed (such as name, age, gender, contact details, etc.) and an alpha-numeric code (barcode) is assigned to my sample in the laboratory, and that (ii) similarly, the results of my sample analysis for clinical genetic testing stored by G42 LABORATORY LLC as per the terms of this consent form are de-identified.
- I understand that if the requested test is not available in-house, my de-identified samples and/or data can be referred to a referral accredited laboratory.
- I understand that my results can indicate **one** of the following:

A POSITIVE MUTATION	A NEGATIVE MUTATION	INCONCLUSIVE RESULTS
In case of a **POSITIVE** result, where genetic changes correlating to the clinical indication of genetic disease are identified thus either confirming either presence of, or predisposition to, the genetic disease, **I understand that further testing may be necessary to confirm the diagnosis.**	In case of a **NEGATIVE** result, where no genetic changes are identified for a suspected disease, **I understand that technical limitations and lack of knowledge of genes may be a contributing factor towards this result.**	In case of an **INCONCLUSIVE** result, where genetic changes are identified but Their association with disease risk is unclear., **I understand that my results will be uninterpretable or of unknown significance.**

- I understand that I have the right to ask questions about my report and to ask for another copy of the report from Biogenix Laboratory, Clinical Genetics Department. I can exercise this right at any time by sending an email to: clinical.genomics.testing@g42.ai
- I understand that my blood sample will be stored only for 7 days, my DNA sample will be stored for 2 years, and my personal data and de-identified data will be stored for a minimum of 25 years, unless as otherwise required by UAE laws.

CONSENT FORM
(Clinical Genomics)

BIOGENIX LABS

- I understand that I am able to withdraw my sample, or personal data, or both from further testing and analysis at any time I please without stating any reasons by emailing clinical.genomics.testing@g42.ai and requesting for a Withdrawal form [BG/REC/GNM/027] which I shall read carefully, fill in the details, sign and send back to withdraw my consent.
- I understand that Biogenix Laboratory abides by the DOH Standard on Patient Healthcare Data Privacy (September 2020), and Abu Dhabi Health Information and Cyber Security (ADHICS) standards.

SECTION II: CONSENT TO SPECIAL PROGRAMS
I read the information leaflet concerning the following program (Kindly tick for the program of choice). I state that the aim, details, advantages and limitations of the selected test(s) have been explained to me by healthcare professional ☐ Premarital genetic screening test ☐ Oncology genetic test ☐ Pre-IVF genetic test ☐ Newborn genetic test ☐ Rare and metabolic genetic test ☐ Other (please specify)

SECTION III: INCIDENTAL FINDINGS	
"Incidental findings" [reported DNA changes that are not related to a clinical indication or a symptom. My report will include my "incidental findings"	☐ Agree ☐ Disagree

SECTION IV: CONSENT TO RESEARCH	
I understand and agree that you and/or your affiliates may use the (i) de-identified raw data which arises out of the sequencing of my sample and (ii) de-identified processed data arising out of the analysis and interpretation of such raw data for research and development purposes, and may share such data with your partners in or outside the UAE for such purposes, in accordance with the laws of the Emirate of Abu Dhabi and the Federal laws of the UAE.	☐ Agree ☐ Disagree

SECTION V: PATIENT DECLARATION OF CONSENT			
By signing this Informed Consent for clinical genetic testing, I acknowledge that I have read and understood the content of this Consent Form, and that I have had the opportunity to have any additional questions answered by physician or genetics professional. With my signature below, I give my consent to clinical genetic testing (or consent on behalf of the patient for whom I am legal guardian).			
Name of Patient/Legal Guardian	Emirates ID# of Patient	Signature of Patient/Legal Guardian [with date]	Witness/Interpreter

SECTION VI: REFERRING CLINICIAN SIGN-OFF			
I have explained genetic testing to the consenting party. I have addressed the limitations of genetic testing to be performed, based on current data. I confirm that the patient is capable of giving these consents (alternatively that consent was given by a legal guardian of the patient), that all questions of the patient have been answered, that the patient had the necessary time to consider his/her decision to proceed with genetic analysis of the provided sample.			
Name of Referring Clinician	Signature	Date	Witness/Interpreter